# Is vaping an aid for smoking cessation? Review of clinical trials and international recommendations.

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# Conflict of interest

- I declare not having received any kind of payment from the electronic cigarette or tobacco or alcohol or gaming industry
- I received honoraria for presentations at meetings in the last 3 years from Pfizer, manufacturer of varenicline.

# Haut Conseil de la santé publique/High Council of Public Health, France

***Avis***

***relatif aux bénéfices-risques de la cigarette électronique***

# ***Opinion on the benefits and risks of electronic cigarettes***

26 Novembre 2021 published on 3 January 2022

file:///C:/Users/500416/Downloads/hcspa20211126_bnridelacileacdelavdufv%20(17).pdf

# Request of 15 May 2020 from the General Director of Health and MILDECA to update the 2016 opinion on the benefits and risks of electronic cigarettes

- *Question 1 (out of 4) :* Is vaping a smoking cessation aid? If so, what is its role in the smoking cessation strategy? And can vaping be considered a tobacco harm reduction tool?

# Recommendations

**The principle: to differentiate the use of ENDS in health care settings and outside it.**

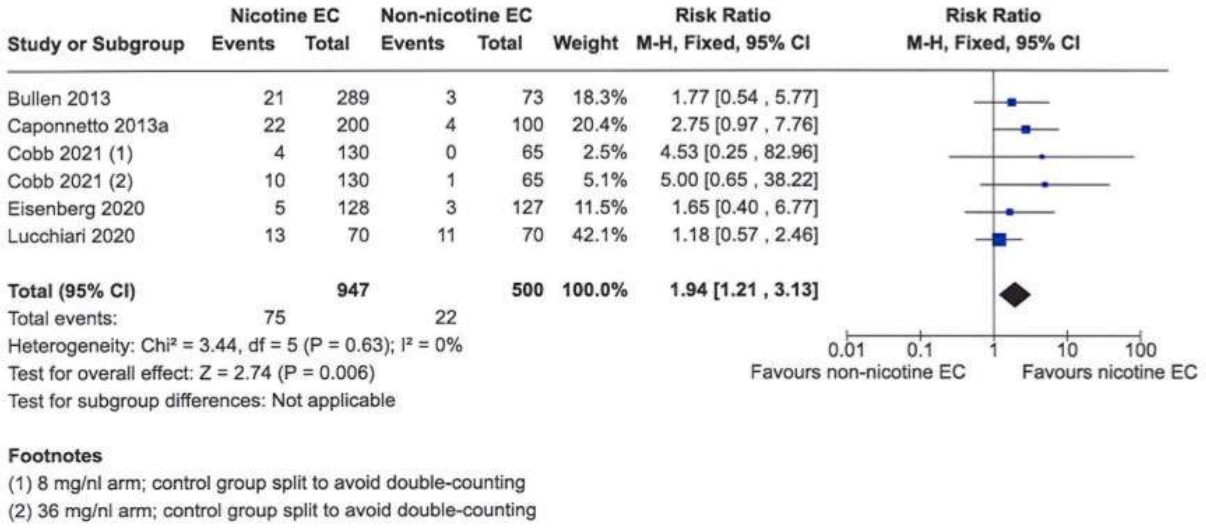
Consumer product *versus* medication/medical device: Evident pharmacological actions of substances delivered by a device and inhaled.

- For health care professionals : compared to therapeutic interventions overall, evidence based knowledge about their therapeutic benefit and associated risk is insufficient **at this stage** to promote their « prescription » by health care professionals. Their promotion by them is not recommended. **Justification:** Recommendation of use by health authorities must be based on in-depth assessment of benefits and risks. This involves knowledge acquisition according to international standards of study design and adverse events' data collection and reporting.
- For the general public: because of the widespread use and potential efficacy in adult smokers, a public health effectiveness cannot be excluded; a reduction in prevalence of smoking is likely.
- Pregnant smokers: because of the lack of straightforward/evidence based benefit/risk data, as always in similar cases, their use is not recommended based on the principle of *nil nocere.*

# Argument

- Statment: it is a strong hypothesis that electronic cigarettes may help smokers quit smoking as a new form of nicotine replacement therapy.

# Meta-analysis of 5 studies in Hartmann-Boyce et al. 2021b ENDS *versus* EDS without nicotine



| Study or Subgroup | Nicotine EC Events | Nicotine EC Total | Non-nicotine EC Events | Non-nicotine EC Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Bullen 2013 | 21 | 289 | 3 | 73 | 18.3% | 1.77 [0.54 , 5.77] |
| Caponnetto 2013a | 22 | 200 | 4 | 100 | 20.4% | 2.75 [0.97 , 7.76] |
| Cobb 2021 (1) | 4 | 130 | 0 | 65 | 2.5% | 4.53 [0.25 , 82.96] |
| Cobb 2021 (2) | 10 | 130 | 1 | 65 | 5.1% | 5.00 [0.65 , 38.22] |
| Eisenberg 2020 | 5 | 128 | 3 | 127 | 11.5% | 1.65 [0.40 , 6.77] |
| Lucchiari 2020 | 13 | 70 | 11 | 70 | 42.1% | 1.18 [0.57 , 2.46] |
| **Total (95% CI)** | | **947** | | **500** | **100.0%** | **1.94 [1.21 , 3.13]** |
| Total events: | 75 | | 22 | | | |

Risk Ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100

Favours non-nicotine EC Favours nicotine EC

Heterogeneity: Chi² = 3.44, df = 5 (P = 0.63); I² = 0%

Test for overall effect: Z = 2.74 (P = 0.006)

Test for subgroup differences: Not applicable

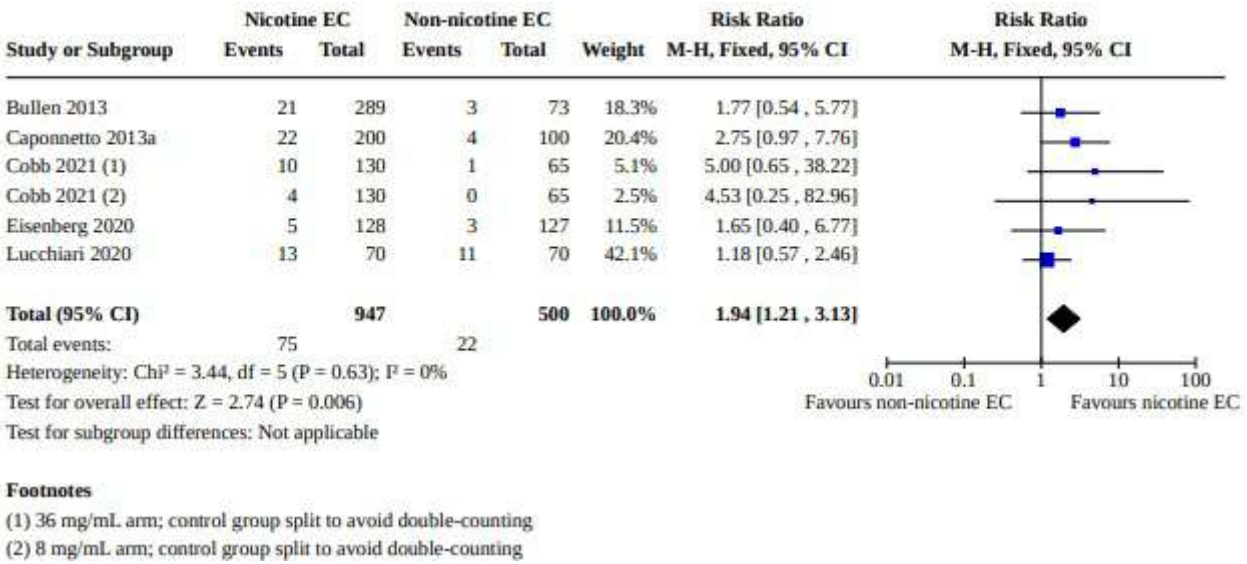
**Footnotes**

(1) 8 mg/nl arm; control group split to avoid double-counting

(2) 36 mg/nl arm; control group split to avoid double-counting

**Individual studies: ENDS=EDS without nicotine/placebo**
**But RR: 1.94 (95%CI:1.21 to 3.13)**

**Analysis 3.1. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 1: Smoking cessation**



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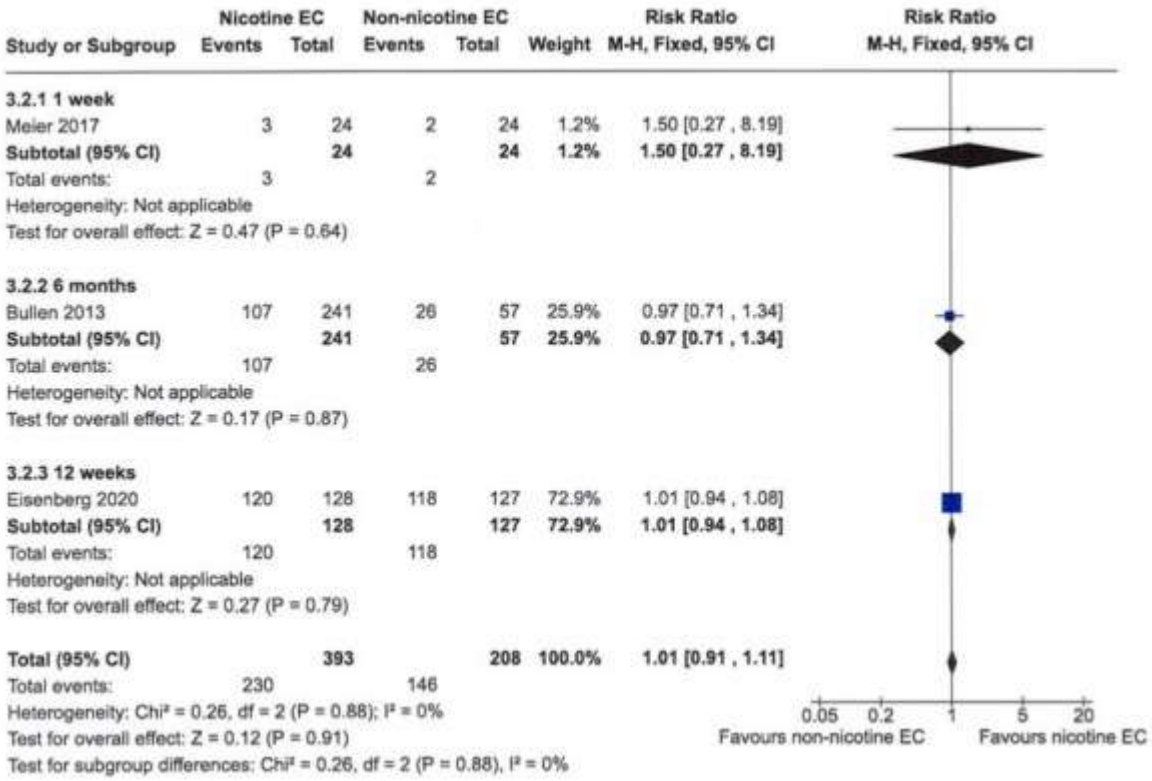
Hartmann-Boyce J et al. **2022**
Published after the Opinion

# Safety: ENDS *versus* EDS without nicotine

3 studies. Bullen et al. 2013 does not provide information about SAE




2 princeps studies

Bullen et al. 2013:

-arms ENDS vs EDS without nicotine blinded

nicotine patch not blinded

-SAE: EC-N:19.7%; EC-Pl: 13.9%; NP: 11.8%

No DSMB, no Medical Dictionary for Regulatory Activities (MedDRA®) reporting

Eisenberg et al.2020: "SAEs were adjudicated by an end points evaluation committee, and the trial was monitored by an external data and safety monitoring board, which conferred before enrollment of the first participant and every 6 months thereafter."

"Serious adverse events and adverse events were obtained via self-report at clinic and telephone follow-ups."

From: **Effect of e-Cigarettes Plus Counseling vs Counseling Alone on Smoking Cessation: A Randomized Clinical Trial**

JAMA. 2020;324(18):1844-1854. doi:10.1001/jama.2020.18889

**Table 2. Adverse Events During the 12-Week Treatment Period by Treatment Group**

| | No. (%) | | |
|---|---|---|---|
| | Nicotine e-cigarettes plus individual counseling (n = 128) | Nonnicotine e-cigarettes plus individual counseling (n = 127) | Individual counseling alone (n = 121) |
| **Serious adverse events[a]** | | | |
| Participants with a serious adverse event | 1 (0.8) | 4 (3.1) | 2 (1.7) |
| Death | 0 | 0 | 0 |
| Respiratory[b] | 1 (0.8) | 0 | 0 |
| Cardiovascular[c] | 0 | 1 (0.8) | 1 (0.8) |
| Neuropsychiatric | 0 | 0 | 0 |
| Other[d] | 0 | 3 (2.4) | 1 (0.8) |
| **Mild adverse events** | | | |
| Participants with an adverse event | 120 (94) | 118 (93) | 88 (73) |
| Cough | 95 (74) | 81 (64) | 66 (55) |
| Dry mouth | 72 (56) | 74 (58) | 55 (46) |
| Headache | 70 (55) | 69 (54) | 46 (38) |
| Rhinitis | 70 (55) | 67 (53) | 51 (42) |
| Throat irritation | 70 (55) | 53 (42) | 30 (25) |
| Dyspnea | 53 (41) | 61 (48) | 43 (36) |
| Sore throat | 44 (34) | 39 (31) | 21 (17) |
| Light headedness | 42 (33) | 34 (27) | 28 (23) |
| Dizziness | 39 (31) | 31 (24) | 37 (31) |
| Mouth irritation | 38 (30) | 24 (19) | 15 (12) |
| Nausea | 37 (29) | 30 (24) | 20 (17) |
| Indigestion | 31 (24) | 33 (26) | 28 (23) |
| Mouth ulcers | 19 (15) | 16 (13) | 7 (6) |
| Vertigo | 16 (13) | 11 (9) | 9 (7) |

Abbreviation: e-cigarette, electronic cigarette.

[a] The denominator used to calculate percentages is the total number of participants randomized to each group. Only the first event for each participant in each category was counted (ie, the numbers represent the number of participants experiencing an event in each category, rather than the absolute number of events). Serious adverse events and adverse events were obtained via self-report at clinic and telephone follow-ups. All documentation obtained pertaining to each reported serious adverse event was independently evaluated by an end points evaluation committee, which determined its potential causal relationship with the study intervention.

[b] One participant in the nicotine e-cigarettes plus counseling group was hospitalized with a chronic obstructive pulmonary disease exacerbation secondary to pneumonia 12 days after being randomized into the trial and had used their e-cigarette in the day preceding the event.

[c] One participant in the nonnicotine e-cigarettes plus counseling group experienced a myocardial infarction 84 days after randomization and had used their e-cigarette in the day preceding the event. One participants in the counseling alone group had critical ischemia in their left leg due to a superficial femoral artery occlusion 43 days after randomization.

[d] Includes 3 participants in the nonnicotine e-cigarettes plus counseling group. One participant experienced both appendicitis and a neoplastic cecal lesion during the treatment period, the second participant experienced epistaxis 39 days after randomization, and the third participant experienced noncardiac chest pain 88 days after randomization. All 3 participants had used their e-cigarette in the day preceding the events. In the counseling group, 1 participant had a urinary tract infection 16 days after randomization.

Adverse Events During the 12-Week Treatment Period by Treatment GroupAbbreviation: e-cigarette, electronic cigarette.

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From: **Effect of e-Cigarettes Plus Counseling vs Counseling Alone on Smoking Cessation: A Randomized Clinical Trial.**

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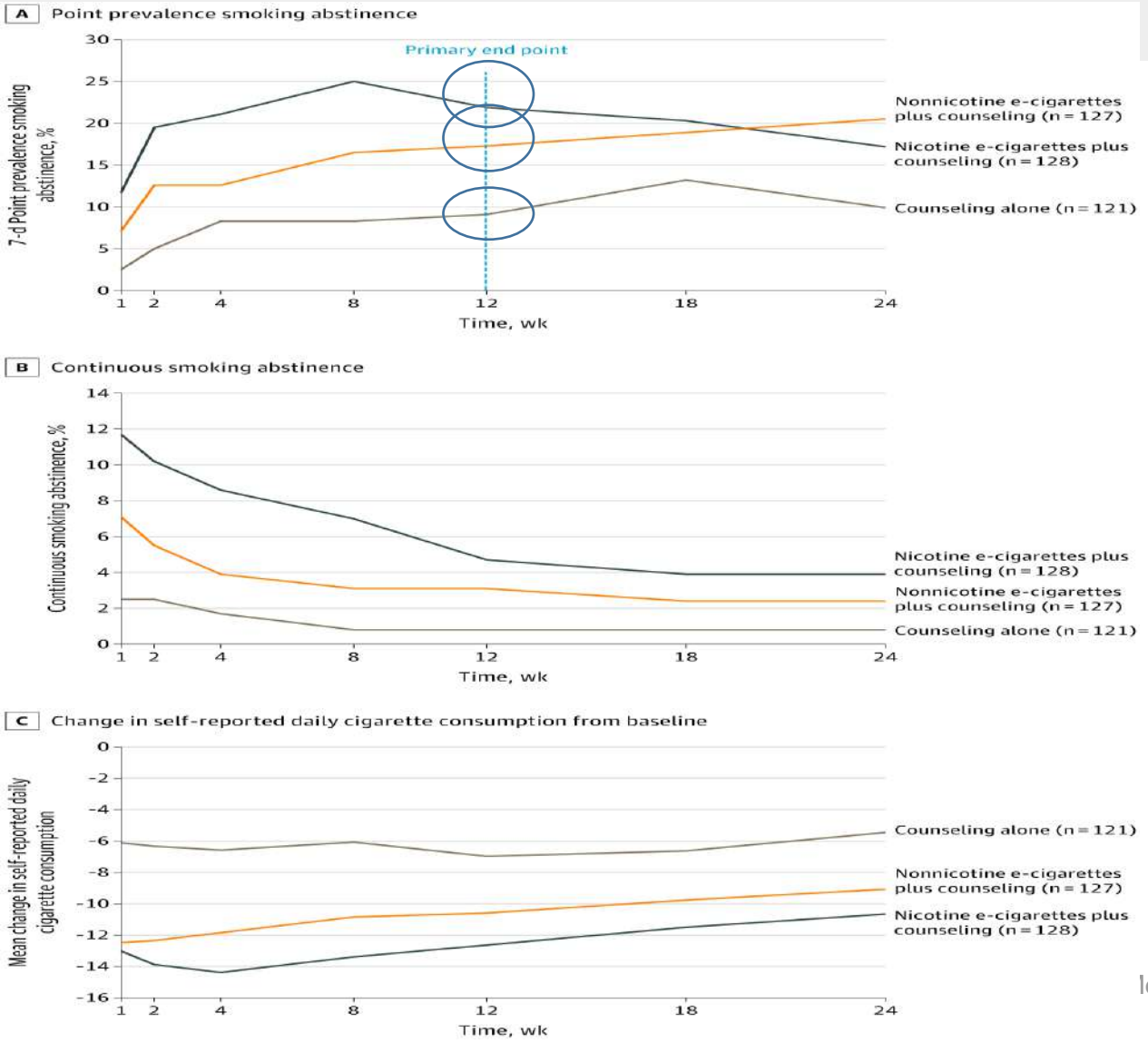


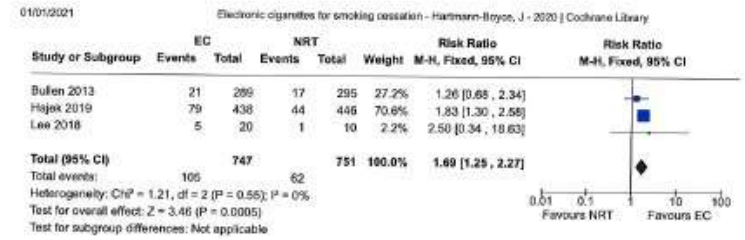

ENDS *versus* EDS without nicotine double blind *versus* counseling only

But placebo > no intervention (Hróbjartsson A Gøtzsche PC Placebo interventions for all clinical conditions. Cochrane Database of Systematic Reviews 2010)

Unfortunately, ENDS = EDS without nicotine as in Bullen et al. 2013

# Comparaisons ENDS *versus* NRT

## Comparison 1: Nicotine EC versus NRT, Outcome 1: Smoking cessation




Aucune comparaison en double aveugle

Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Butler AR, Hajek P. Electronic cigarettes for smoking cessation. Cochrane Database of Systematic Reviews 2020, Issue 10. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub4. Accessed 01 January 2021.

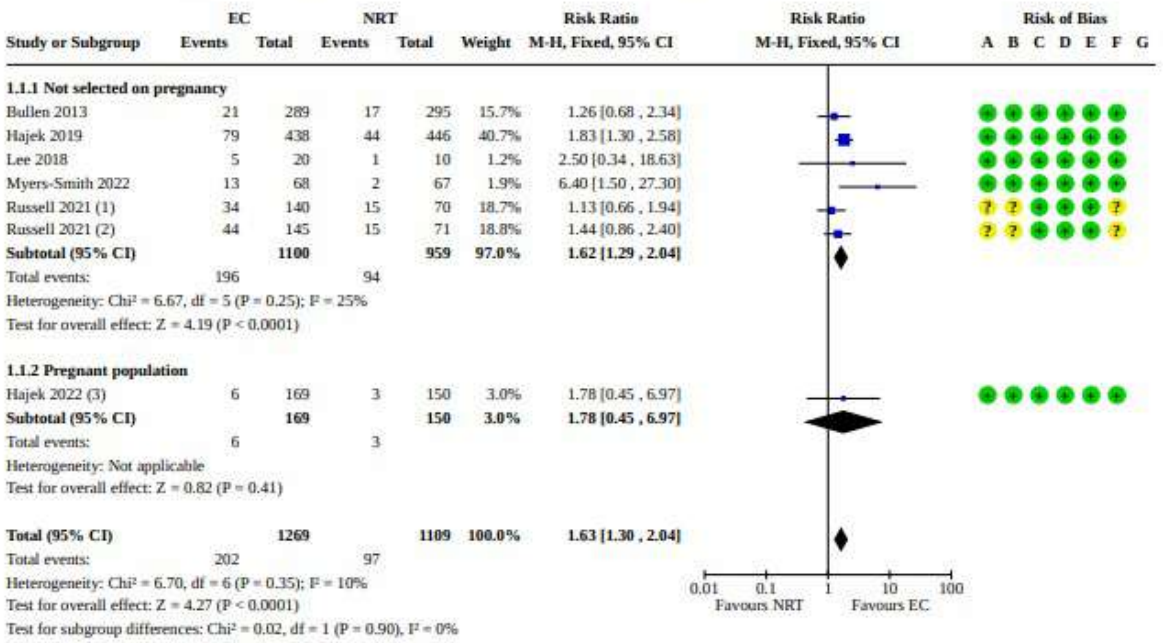
Hartmann-Boyce et al. 2021b

3 studies

**RR: 1.69, 95% CI 1.25 to 2.27 (ENDS > NRT)**

All are open label comparisons.
Treatment adherence ENDS>>NRT
Only Hajek et al. 2019 shows ENDS>NRT
Russel 2021 seems to be an abstract.

**Analysis 1.1. Comparison 1: Nicotine EC versus NRT, Outcome 1: Smoking cessation**




New study

Pregnant smokers

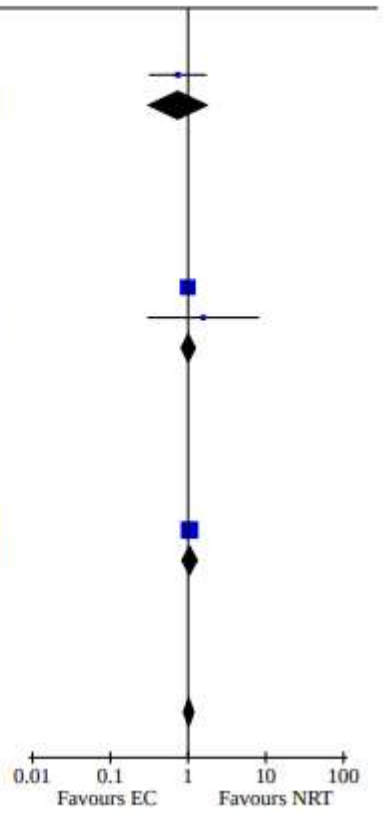
Published after the Opinion

Hartmann-Boyce J, Electronic cigarettes for smoking cessation. Cochrane Database of Systematic Reviews **2022**, Issue 11. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub7.

**1.62, 95% CI 1.29 to 2.04 (ENDS > NRT)**

**Analysis 1.2. Comparison 1: Nicotine EC versus NRT, Outcome 2: Adverse events**

| Study or Subgroup | Nicotine EC Events | Nicotine EC Total | NRT Events | NRT Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **1.2.1 4 weeks** | | | | | | |
| Lee 2018 (1) | 7 | 19 | 5 | 10 | 2.9% | 0.74 [0.31 , 1.73] |
| **Subtotal (95% CI)** | | **19** | | **10** | **2.9%** | **0.74 [0.31 , 1.73]** |
| Total events: | 7 | | 5 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.70 (P = 0.48) | | | | | | |
| **1.2.2 6 months** | | | | | | |
| Bullen 2013 | 107 | 241 | 96 | 215 | 44.4% | 0.99 [0.81 , 1.22] |
| Myers-Smith 2022 | 4 | 60 | 2 | 47 | 1.0% | 1.57 [0.30 , 8.19] |
| **Subtotal (95% CI)** | | **301** | | **262** | **45.4%** | **1.01 [0.82 , 1.24]** |
| Total events: | 111 | | 98 | | | |
| Heterogeneity: $Chi^2 = 0.29$, df = 1 (P = 0.59); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 0.06 (P = 0.95) | | | | | | |
| **1.2.3 3 months after end of pregnancy** | | | | | | |
| Hajek 2022 | 124 | 556 | 118 | 554 | 51.7% | 1.05 [0.84 , 1.31] |
| **Subtotal (95% CI)** | | **556** | | **554** | **51.7%** | **1.05 [0.84 , 1.31]** |
| Total events: | 124 | | 118 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.40 (P = 0.69) | | | | | | |
| **Total (95% CI)** | | **876** | | **826** | **100.0%** | **1.02 [0.88 , 1.19]** |
| Total events: | 242 | | 221 | | | |
| Heterogeneity: $Chi^2 = 0.93$, df = 3 (P = 0.82); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 0.26 (P = 0.80) | | | | | | |
| Test for subgroup differences: $Chi^2 = 0.62$, df = 2 (P = 0.73), $I^2 = 0\%$ | | | | | | |




Hartmann-Boyce J et al. 2022
4 studies
None reports on DSMB, MedDRA® reporting

**Conclusion Cochrane Review 2022:**

"There is high-certainty evidence that ECs with nicotine increase quit rates compared to NRT and moderate-certainty evidence that they increase quit rates compared to ECs without nicotine."

Remarks:

1. How is it possible that the difference is greater *versus* NRT – reference treatment – than *versus* placebo/nothing? Usually: no intervention<placebo<reference treatment ≤ new treatment (non-inferiority or superiority trials).

2. Experimental design : only two arms of two double-blind studies, the other studies and arms are open comparisons (inherent to pragmatic studies) – the preference for ENDS may explain the superiority – compliance of ENDS >> NRT.

Pragmatic trials versus double blind/double dummy RCT?
AE reporting according to international standards?

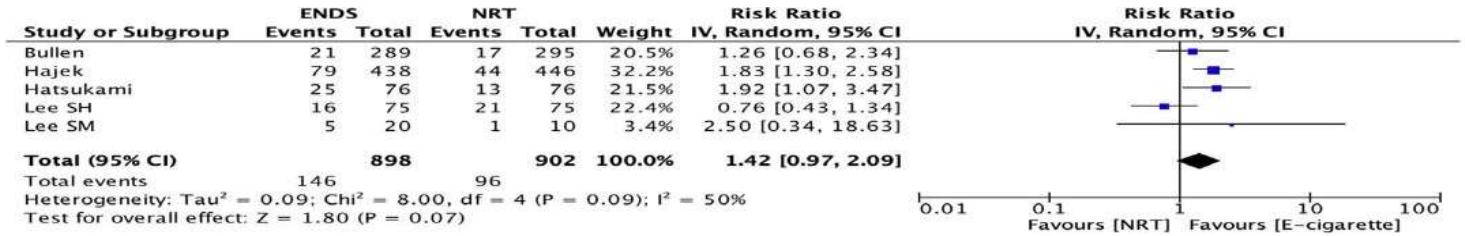
Catherine M Pound et al. BMJ Open 2021;11:e044222

Published after the Opinion

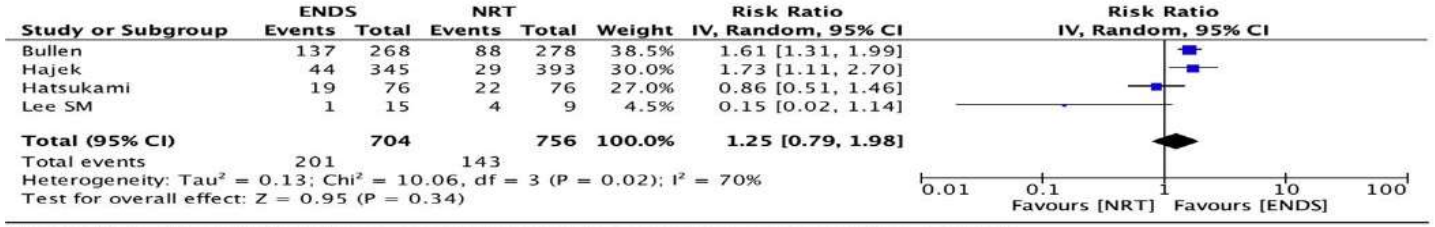
**Pooled results per outcome.**

**From Ottawa, Canada**

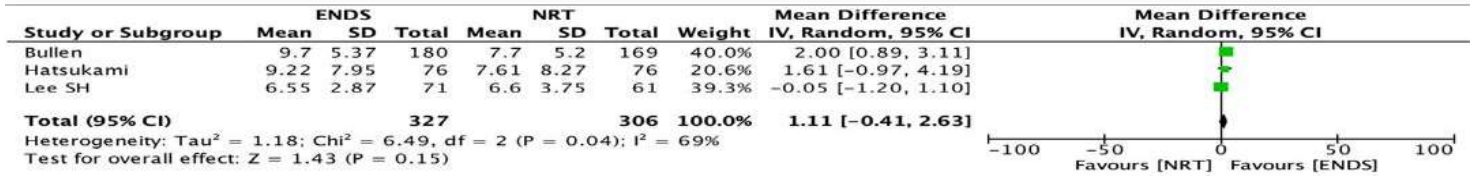
## ENDS vs NRT



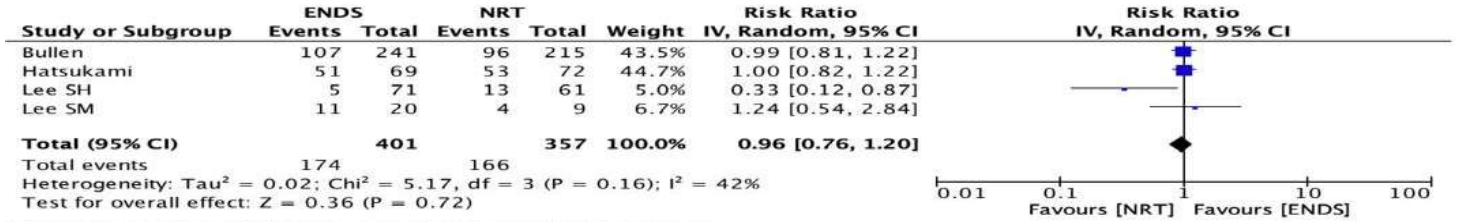

**Smoking cessation outcome**




**Proportion of participants successfully reducing smoking consumption by 50%**




**Mean reduction of cigarettes from baseline**




**Proportion of participants experiencing adverse events**

4 études

**RR: 1.42, 95% CI 0.97 to 2.09**

**(ENDS=NRT)**

Consumption reduced by 50% =

CPD reduction =

% of AE =

# Recommendations from other countries as reported in the Opinion

Health Research Board, Ireland : Electronic cigarette and smoking cessation. An evidence review. Published on 12 October 2020. https://www.hrb.ie/publications/publication/electronic-cigarette-and-smoking-cessation-an-evidence-review/returnPage/1/Accès le 17 janvier 2022. Authors: Joan Quigley, Helen Kennelly, Caitriona Lee, Doireann O'Brien, Michelle Williams, Anne McCarthy, Jean Long

- Seven RCTs met the inclusion criteria for efficacy of e-cigarettes in helping people quit smoking and nine provided data for safety.
- The systematic review and network meta-analysis of e-cigarettes versus therapies usually given for smoking cessation showed that there is **no evidence of a difference in effect on incidences of smoking cessation**.
- **There is a low-level of certainty in these results due to low successful event rates and high rates lost to follow-up in all studies**.
- We identified respiratory adverse events, including shortness of breath and cough, that appeared to be higher in e-cigarette users, but in the main, **RCT evidence on adverse events is lacking**.
- **The long-term data on e-cigarettes, in line with European Medicines Agency recommendations, are limited for both smoking cessation and adverse events**, and further **large-scale research using a standardised product to decrease uncertainly at the 1-year timepoint and beyond is needed**.

Leone FT, Zhang Y, Evers-Casey S, Evins AE, Eakin MN, Fathi J, Fennig K, Folan P, Galiatsatos P, Gogineni H, Kantrow S, Kathuria H, Lamphere T, Neptune E, Pacheco MC, Pakhale S, Prezant D, Sachs DPL, Toll B, Upson D, Xiao D, Cruz-Lopes L, Fulone I, Murray RL, O'Brien KK, Pavalagantharajah S, Ross S, Zhang Y, Zhu M, Farber HJ. Initiating Pharmacologic Treatment in Tobacco-Dependent Adults. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2020 Jul 15;202(2):e5-e31. doi: 10.1164/rccm.202005-1982ST. PMID: 32663106; PMCID: PMC7365361.

- Question 4: For Tobacco-Dependent Adults in Whom Treatment Is Being Initiated, Should Treatment Be Started with Varenicline or an Electronic Cigarette?
- For tobacco-dependent adults in whom treatment is being initiated, we suggest varenicline over electronic cigarettes (conditional recommendation, very low certainty in the estimated effects). Remarks: The recommendation's strength reflects very low certainty in the effects used to derive the recommendation. After our evidence synthesis, new evidence emerged regarding serious adverse effects of electronic cigarettes. If these serious adverse effects continue to be reported, the strength of the recommendation should be reevaluated. **Note that this recommendation is intended for treatment of tobacco dependence under the supervision of a clinician; it should not be extrapolated to unsupervised treatment or recreational use.**

US Preventive Services Task Force, Krist AH, Davidson KW, Mangione CM, Barry MJ, Cabana M, Caughey AB, Donahue K, Doubeni CA, Epling JW Jr, Kubik M, Ogedegbe G, Pbert L, Silverstein M, Simon MA, Tseng CW, Wong JB. Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Persons: US Preventive Services Task Force Recommendation Statement. JAMA. 2021 Jan 19;325(3):265-279. doi: 10.1001/jama.2020.25019. PMID: 33464343.

The USPSTF concludes that **the evidence on the use of e-cigarettes for tobacco smoking cessation in adults, including pregnant persons, is insufficient, and the balance of benefits and harms cannot be determined.** The USPSTF has identified the lack of well-designed, randomized clinical trials on e-cigarettes that report smoking abstinence or adverse events as a critical gap in the evidence.

United States Public Health Service Office of the Surgeon General; National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. Smoking Cessation: A Report of the Surgeon General [Internet]. Washington (DC): US Department of Health and Human Services; 2020. PMID: 32255575.

- E-cigarettes, a continually changing and heterogeneous group of products, are used in a variety of ways. Consequently, it is difficult to make generalizations about efficacy for cessation based on clinical trials involving a particular e-cigarette, and there is presently **inadequate evidence to conclude that e-cigarettes, in general, increase smoking cessation**.

WHO report on the global tobacco epidemic, 2021: addressing new and emerging products: executive summary
17 August 2021
https://www.who.int/publications/i/item/9789240032842

- The focus of this report, addressing new and emerging products, charts a new threat to tobacco control. **ENDS are increasingly available in many countries along with other novel products like heated tobacco products and nicotine pouches.** As they emerge and rapidly evolve, these products can be difficult to characterize and therefore bring with them many regulatory challenges. At the same time, the tobacco and related industries behind these newer products pedal misinformation campaigns, marketing them as “clean”, “smokefree” or “safer”, and **claim they are effective cessation aids**. By doing so, these industries attempt to appear part of the solution to the tobacco epidemic, as opposed to instigators and perpetrators of the epidemic.

The European Commission and its Scientific Committee on Health, Environmental and Emerging Risks (SCHEER), final Opinion on electronic cigarettes. https://health.ec.europa.eu/system/files/2022-08/scheer_o_017.pdf

- Regarding the role of electronic cigarettes in cessation of traditional tobacco smoking, the SCHEER concludes that there is **weak evidence for the support of electronic cigarettes‘ effectiveness in helping smokers to quit while the evidence on smoking reduction is assessed as weak to moderate.**

https://solidarites-sante.gouv.fr/prevention-en-sante/addictions/produits-de-vapotage-cigarette-electronique/article/recommandations-concernant-l-usage-des-produits-de-vapotage-cigarette
26/9/2022

- **Recommandations concernant l'usage des produits de vapotage / cigarette électronique**

MINISTÈRE
DE LA SANTÉ
ET DE LA PRÉVENTION
*Liberté*
*Égalité*
*Fraternité*

MINISTÈRE
DES SOLIDARITÉS,
DE L'AUTONOMIE
ET DES PERSONNES
HANDICAPÉES
*Liberté*
*Égalité*
*Fraternité*

Specific website for general reporting of symptoms and health disorder occuring during and after use.

# Merci de votre attention